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September 17, 1999

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Draft Guidance for Industry on Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action [Docket No. 99D-1783].

Dear Sir/Madam:

On behalf of the Science Committee of the Generic Pharmaceutical Industry Association (GPIA), I am forwarding comments on "Draft Guidance for Industry on Bioavailability and Bioequivalence Studies, for Nasal Aerosols and Nasal Sprays for Local Action", 64 FR 33869, June 24, 1999.

GPIA is comprised of the manufacturers and distributors of generic medicines (as well as The providers of technical services and goods to these firms.) Many of our members will be directly impacted by implementation of the subject draft guidance.

Thank you for the opportunity to submit our comments on the subject draft guidance. We Would appreciate your consideration of these comments as you finalize the guidance.

Sincerely,

Alice E. Till, Ph.D.
President

Cc: B. Brannan, Co-Chair, GPIA Science Committee
C. Pelloni, Co-Chair, GPIA Science Committee
D. Miran, Chair, GPIA Topicals Taskforce
W. Adams, CDER, FDA (via mail and e-mail)

99D-1738

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General Comments

1. Standard ICH nomenclature should be employed where practical. An example would be to use Active Pharmaceutical Ingredient (API) and not drug substance.
2. Wherever possible this guidance should refer to other specific guidance's and not repeat sections from them. This will greatly simplify revision and make use of the guidance easier for all concerned.
3. It is extremely useful when commenting on draft guidance's if the line numbers are given in the left margin. We recommend that all draft guidance's use this convention.
4. It would be extremely useful if the Agency could indicate which, if any, of the *in-vitro* tests described in this guidance would, in its current thinking, be useful in evaluating the bioequivalence of a centrally acting nasal spray for which there are measurable blood levels.
5. The need for a separate study to demonstrate that the packaging and the formulation are compatible is not included in the guidance. Such a study is a key part of the development of a suitable nasal spray. Such a study involves the exposure of the various components making up the pump system to the formulation or formulation vehicle to determine if any materials are extracted from the packaging. Such a study can be conducted using stress conditions, such as 55° C for a month, to keep it to a reasonable time frame. GC and HPLC can then be used to examine the samples. A protocol for such a study will be provided if desired.
6. We would like to request guidance on how a generic manufacturer can conduct a dose-linearity study on a product that has a dose of one spray. Would it be acceptable to prepare product at ½ or ¼ strength for the purposes of these studies? Would this be satisfactory even though this is not the actual product?

Specific Comments

Section II.A.2. Last sentence first paragraph: The decision tree is on page 32, not page 35.

Section III.A. This section requires that for an ANDA for a suspension "...the PSD of the active drug in the dosage form should be the same as that of the reference listed drug." It also asks the ANDA sponsor to supply comparative information on the "morphic form", "size and number of drug aggregates", and "hydrous form".

These are unreasonable and potentially insurmountable barriers to generic Manufacturers. Furthermore, they contradict information provided earlier in the guidance. On page 4 first paragraph it refers to "...the inability to adequately characterize drug PSD..." indicating the requirement to provide such data is simply not possible.

Any attempt to isolate the particles from the suspension could cause changes in the morphic form, particle size distribution, or hydrous form.

Information on the morphic form is not generally available, and at best would be limited to a microscopic evaluation of the general shape of the particles. The same is true for the number and size of aggregates. The only information available regarding the hydrous form would be from the product label. By definition, the generic manufacturer must use the same active ingredient and a match of the hydrous form or solvate to the label is sufficient.

Therefore we recommend the paragraph be reworded to replace the middle three sentences with the following.

"For an ANDA of a suspension formulation, data demonstrating the comparable PSD and morphic form of the drug particles, size and number of drug aggregates in the dosage form, and the hydrous or solvate form of the active drug in the dosage form to the reference listed drug, should be provided where possible. Where this is not possible a list of the attempted studies should be provided."

Section III.B. The requirement that "A test product should attain prime within the labeled number of actuations for the reference product" is not always possible and could present an insurmountable barrier to the generic manufacturer.

Some products have proprietary bottles and/or pumps. The pump manufacturer for the RLD can not provide the identical pump, and there are no expiration dates for these types of agreements. The generic manufacturer can try and obtain as close a match as possible, but there may sometimes be unavoidable differences. The differences in dip tube length required because of differences in bottles, or minor changes in the pump chamber, may impact the number of actuations required to attain prime. Therefore, we recommend the sentence be reworded as follows:

"A test product should attain prime with the labeled number of actuations for the reference product, whenever possible. When this is not possible, a thorough explanation and justification as well as the required change in labeling must be submitted for consideration."

Section IV.A. The last sentence in this section recommends discussions with the Agency regarding BE studies. Pre-ANDA discussions with OGD are extremely difficult to arrange and can take up to 6 months to schedule when they do occur. Therefore, we request that a mechanism be established to promptly schedule meetings with OGD to discuss BE protocols or that specific guidances be published.

Section IV.B.1. The requirement for qualitative (Q1) and quantitative (Q2) identity in order to rely solely on *in-vitro* tests for BE is overly restrictive. Changes in items such as excipients or preservatives, which do not change the pump performance characteristics, should be permitted unless there is evidence, such as in the peer reviewed literature, that these ingredients impact bioavailability.

The first sentence on page 7 indicates that “essentially the same” means all inactive ingredients are within +/- 5% of the amount in the reference listed drug. For simple solutions the entire purpose of the guideline is to establish that the pump performance characteristics, and therefore the products, are essentially the same. We suggest that for changes that are larger than 5%, where there are no safety issues, the limits of changes be based on changes that might effect pump performance, such as a change of viscosity or surface tension of greater than 5%.

In-vivo tests are not required, but if they are completed and demonstrate therapeutic equivalence, this should over-ride the *in-vitro* results. Such results may be the evidence needed to demonstrate that the criteria for bioequivalence by the *in-vitro* tests could be relaxed.

Section IV.B.2. To document BE, *in-vivo* studies should include both a pharmacokinetic study and a BE study with a clinical endpoint. The pharmacokinetic study is meant to document systemic exposure. The document should better define the aim of this particular study. Clinical exposure is assessed to assure that undesirable systemic effects from the test product are no worse than the undesirable systemic effects from the reference product. We would like to suggest that the statistical criterion reflect this objective. The objective of this study is not to “establish equivalent systemic absorption”, rather it is to establish that absorption is not statistically significantly greater, or is no more than for example 25% greater. Therefore our suggestion would be to set an upper limit in order to protect the subject from a greater exposure as opposed to setting a confidence interval limit.

At the workshop in Washington in June, somebody asked what would be the standards that would need to be met for that study? The answer was that probably, it would be the same as for a regular bio study with mean ratios and 90% CI for AUC_t, AUC_{inf} and C_{max}. Prior discussion with FDA indicated that about 18 subjects would be sufficient to address the issue of systemic exposure. A final decision needs to be made by the agency and the decision criteria need to be defined in this guidance.

The statement that the “Inactive ingredients also should be qualitatively (Q1) the same and quantitatively (Q2) essentially the same as the inactive ingredients in the reference listed drug...” is overly and needlessly restrictive. If there are changes in non-critical ingredients, such as preservatives, the equivalence of the products should be demonstrated by the studies required in this guidance.

If the same drug substance is approved for oral dosing, the approved oral dose can be compared to the maximum dose that could be swallowed from the approved nasal spray/aerosol dose. If the approved oral dose is higher than the oral dose possible from the nasal product, no *in vivo* study of systemic exposure from the nasal product should be necessary.

Section IV.B.3. The statement that the "...inactive ingredients also should be qualitatively (Q1) the same and quantitatively (Q2) essentially the same as the inactive ingredients in the reference listed drug..." is overly and needlessly restrictive. If there are changes in non-critical ingredients, such as preservatives, the equivalence of the products should be demonstrated by the studies required in this guidance.

If therapeutic equivalence is established by appropriate *in-vivo* studies but the statistical criteria for equivalence is not met for the *in-vitro* studies, the guidance indicates that a suspension product will not be considered bioequivalent. In the absence of any relationship between the equivalence criteria for the *in-vitro* tests and the therapeutic equivalence of the products (their qualification for an AB rating), it is not logical to find such products to be therapeutically inequivalent. These bioequivalence criteria set for *in-vitro* tests are more stringent than the quality assurance criteria.

Section IV.C. The statement that no guidance is available for SUPAC type changes adds nothing to the guidance. Please consider either deleting that sentence or providing meaningful guidance.

Section V.B. The reference at the top of page 10 should be to page 32.

Blinding when using automated actuators is impractical because the mechanism must be reset to address even small differences in bottle height. The blinding of post-actuation evaluations should only apply to manual determinations where the lack of blinding could impact the decision process. Therefore, we recommend the following three changes in the first full paragraph on page 10.

- Reword the second sentence to read as follows: "BE tests should be conducted in a manner that removes potential analyst bias, e.g., employ automated or blinded procedures."
- Reword the next to last sentence as follows: "Manual post-actuation evaluations should be conducted employing blinded procedures, where possible."
- Reword the last sentence as follows: "The mechanisms employed to assure a lack of bias in the data should be explained. If blinding is employed, the randomization procedure should accompany the submission. All test methods or SOPs for each test should accompany the data in the submission."

Section V.B.1. The title of this section should reflect consistent terminology based on the test required (see discussion below on dose.) Therefore it should be either *Dose Content Uniformity Through Container Life* or *Spray Content Through Container Life*.

While the desire to assure dose uniformity, which could be impacted by product non-uniformity, could require the actual assay of a suspension product delivered through the pump, this requirement is excessive for solution products. A packaging compatibility study as described above would negate the need to assay each spray and allow the use of the weight per actuation for these studies of solution products. For ANDA comparisons, it can be assumed that the approved reference listed product would also meet this requirement.

The sentences in the middle of this paragraph misuse the term dose in an attempt to define a test method. A minimum dose is the minimum number of sprays actuated into the patient at a single time. If the label says to actuate one spray into each nostril the dose is two sprays. Therefore, we suggest that the term be used correctly, as that is what is relevant to the patient and the second sentence should be reworded as follows:

“A single dose represents the minimum number of sprays specified in the labeling.” Or if the intent is to have the test based on the minimum number of sprays rather than the patient dose, then the following wording should replace both sentences. “The number of sprays per determination should not exceed the minimum number of sprays per nostril specified in the labeling.”

The next to last sentence in this section reads “Analytical data should be validated, and the analytical validation report should accompany the content uniformity report.” Analytical methods, not data, are validated. The test discussed in this section is Spray Content Uniformity through Container Life and not content uniformity. Therefore, the sentence should be reworded as follows, “Analytical methods should be validated, and the analytical method validation report should accompany the spray content uniformity through container life report.”

Section V.B.2. In the next to last line of this section it states “...PSD characterization cannot be acceptable validated...” and in the following line it states “...PSD studies should be performed, and these supportive characterization data, along with available validation information should be submitted.” It is unreasonable to request unvalidatable data, which then becomes part of the approval decision process. This would appear to be an attempt to collect data for potential future use and is more appropriate as part of a PQRI initiative. The development of standardized test methods and the validation of these methods would seem to be the kind of item in which the USP has the greatest expertise. It is suggested that they be requested to undertake such an effort with the help of industry.

We recommend that this entire section be replaced with a request that, within instrument and apparatus capability, it be demonstrated that each pump delivers greater than 90% of the dose in droplets greater than 9 (or 10) microns. This would assure that the dose is delivered to the nose and not to the lungs. The data to support this test should also be provided. A single stage impactor, or a single stage in the cascade impactor would be adequate for this purpose and greatly simplify the test procedure.

Section V.B.2.a. The laser diffraction methodology specified under Droplet Size Distribution is not validatable per the instrument manufacturer. This equipment requires periodic calibration. So the appropriate wording should be “...*validated* or *calibrated* alternate...”

In the last sentence on page 11 the statement that PSD (particle size distribution) should be determined for whether a product is “formulated as solution” is inappropriate and scientifically incorrect. Solutions do not contain particles. Rather the impactor or impinger determines the apparent size of the droplets formed by the pump. The subsection should be reworded as follows: “For all nasal aerosols and nasal sprays, the distribution of the spray by size, as

determined by a multistage cascade impactor (CI) or a multistage liquid impinger (MSIL), should be provided.” Please also note the previous comment that a single stage apparatus is sufficient for nasal sprays.

The entire section entitled Drug and Aggregate PSDs should be deleted. As previously stated there are no methods for properly evaluating these parameters. Light microscopy is only suggested for the purposes of estimating. Therefore, there is no criteria for comparison and any differences detected would be uninterpretable, so no meaningful data will be obtained. Significant amounts of aggregation would be expected to impact homogeneity, which would be detected via the required unit spray content test and potentially via the laser diffraction method.

The request in the section on laser diffraction that “All instrument/computer printouts should be submitted. . .” is excessive and inconsistent with the Paperwork Reduction Act, Good Regulatory Practices and the recent decision to no longer require submitting all case report forms. For a typical study, as outlined previously in this guidance, the data would include over 500 pages. These data are reviewable during a pre-approval inspection, and can be submitted when specifically requested. Therefore, we recommend rewording this requirement to be consistent with current practices for case report forms as follows: “A representative 5% sample of the instrument/computer printouts should be submitted. . .”

The Group 1 requirements documented in the second paragraph in the section on Multistage Cascade Impaction are unnecessary in this guidance. These items are components of MDI's and are not used with nasal sprays, and therefore should be dropped from this guidance.

For nasal products, two stages which define the respiratory fraction and the non-respiratory fraction are sufficient. A twin stage impactor as described in the USP is adequate for this purpose. Therefore, this entire section should be rewritten to limit the testing to achieve this goal.

Continuing in the same section, mass balance is never exactly 100%. Guidance should be provided as to what ranges would meet the requirement to demonstrate mass balance. Additionally, the proposed limit on the number of sprays permitted in the study, which is limited to “generally not exceeding 10”, can directly contradict the need to achieve mass balance for stages with very low deposition. When the conflict arises between mass balance and 10 sprays which is the preferred course of action?

Section V.B.3. The requirement for determination of spray pattern at three distances is excessive, unnecessary and a carry over from metered dose inhalers. In fact, the pump manufacturers are recommending a single distance. The distances that are relevant for nasal sprays are extremely short and therefore, two distances are adequate.

The drug substance specific visualization requested is not always achievable, particularly at longer distances, so the following wording is suggested. “The visualization technique should be specific for the drug substance, where possible. Where this is not possible, a summary of the experiments attempted should be submitted and ‘spray’ specific visualization technique employed.”

Since what is relevant to the patient is the dose to a given nostril, and not necessarily a single spray, we recommend the following rewording. "Spray patterns should be determined on the minimum dose per nostril listed in the product labeling..."

The request "Clear, legible photographs or photocopies of spray patterns...should be provided", is excessive and inconsistent with the Paperwork Reduction Act, Good Regulatory Practices and the recent decision to no longer require submitting all case report forms. This data is available for review during a pre-approval inspection, and can be submitted when specifically requested. Therefore, we recommend rewording this requirement to be consistent with current practices for case report forms as follows:

"A representative sample of clear, legible photographs or photocopies of spray patterns...should be provided."

Section V.B.4. The requirement for determination of plume geometry at three distances is excessive, unnecessary and a carry over from metered dose inhalers. The distances that are relevant for nasal sprays are extremely short and therefore, two distances are adequate. The shape of the plume at distances or time that are beyond even the largest nasal cavity is meaningless.

Section V.B.5. The statement is made that "Priming and repriming data provides information to ensure delivery of the labeled dose of drug, and thus are part of the in-vitro BA and BE assessment." Making sure the drug meets the label claim is clearly a CMC and labeling issue, and not a bioequivalence or bioavailability issue. Therefore, we believe this issue belongs in the CMC guidance.

At times there may be situations where an ANDA submission will be unable to follow the same labeling as the reference listed drug due to insurmountable barriers (i.e., proprietary agreements with the pump manufacturer on chamber size, orifice design, etc.). Thus we suggest that the following wording be added. "For products approved under an ANDA, the labeling is the same as that for the reference listed drug, except for specific changes described in the regulations (21CFR314.94(a)(8)(IV) or with adequate justification for changes where appropriate."

The testing of priming and repriming in multiple orientations for an ANDA submission is unnecessary. The reference-listed drug has provided a standard for comparison in its labeling. The generic version should only be required to duplicate the labeled requirements of the reference listed drug product and all comparisons should be on that basis. What is the meaning if the generic product is not equivalent in an orientation outside of the labeling?

Section V.B.6. Tail-off is a labeling and CMC issue, and not a BE/BA issue. Small changes in dip tube length or product orientation can impact the shape of the tail-off curve. Comparison of these curves is subjective and, even in a supportive role, uninterpretable. Therefore we recommend that this section be deleted from this guidance.

Sections VI&VII&VIII. For the purposes of clarity and consistency we recommend the following titles be used.

VI. Bioequivalence (BE) Clinical Study Demonstrating Local Delivery

VI.D. Study Designs and Subject Inclusion Criteria for BE Study Demonstrating Local Delivery

VII. Design and Subject Inclusion Criteria for Systemic Exposure Study for Locally Acting Nasal Aerosols and Sprays for which Blood Concentrations may be Demonstrated

VIII. Design and Subject Inclusion Criteria for Systemic Exposure Study for Locally Acting Nasal Aerosols and Sprays for which Blood Concentrations May Not Be Demonstrated

Section VI.A., D. In VI.A., the second sentence reads, "Although BA and BE studies with a clinical endpoint are sometimes incapable of showing a dose-response relationship..." In VI.D., the first sentence reads, "A BE study with a clinical endpoint to establish equivalent local delivery of drug from test and reference products to the nose should document sensitivity of the study to discriminate between differing doses (i.e. show a dose-response relationship)." These two statements are in direct conflict. First it is stated that a dose-response relationship cannot be shown in these studies, then it is stated that one must be shown.

Section VI.D goes on to suggest that the second dose may be lower than the one at which equivalence is to be compared. Demonstration of a difference between the two doses does not support the dose-response requirements of a pharmacological endpoint study at the higher dose.

The requirement of a dose-response relationship to establish that equivalence is tested on a rising portion of the dose-response curve and not in the EMAX range of doses, is logical for a pharmacological endpoint study. A clinical endpoint frequently consists of a collection of pharmacological and physiological and biochemical actions in response to uncontrolled allergen exposure and controlled drug exposure. It is not surprising that the clinical endpoint bears no simple (dose-response) relationship to the drug exposure (dose).

Section VI.B. For the sake of clarity we suggest that the second sentence in this section start "For covered antihistamines and corticosteroids efficacy..."

Section VI.D. On page 18 it indicates that a protocol should be submitted for review at FDA. There does not appear to be a mechanism for timely review of submitted protocols within OGD. Can a mechanism be created to facilitate the submission and review of these protocols? Otherwise, this becomes a significant barrier to the generic industry.

The following wording for the first two sentences in this section is suggested for the sake of clarity. "A BE study with a clinical endpoint should be used to establish equivalent local delivery of drug from test and reference product to the nose. The sensitivity of the study to discriminate between differing doses (i.e., show a dose-response relationship) should be explored.

It is also recommended that for clarity the following sentence be added at the end of the paragraph. "As noted in Section VI.A. it may be impossible to show a dose-response relationship."

In the second sentence of this section, it is stated that the documentation typically relies on the inclusion of a second dose of the reference product that may be higher or lower to demonstrate that the efficacy response is different between the two doses. We do not always agree with this statement of the guidance, as the demonstration of a difference between the two doses may not support the dose-responses requirement at the higher dose.

Because of the variability of the outcome measurements, for example the rhinitis score for a nasal corticosteroid suspension formulation, it might be necessary to recruit a large number of subjects per group. We would like to bring to the attention of the agency that to fulfill their requirements a minimum of 400 patients might be necessary for a 4-leg parallel study (placebo, Test, Ref 1, Ref 2) with at least 100 subjects per leg.

On page 19 (VI.D.3) an Environmental Exposure Unit (EEU) Study is discussed. There might be an ethical issue with some Institutional Review Board Committees with regards to the use of patients in this type of study.

Section VII. In the first paragraph there is the statement that the protocol should be discussed with the “review staff prior to the study.” There is no provision for a pre-ANDA meeting with OGD to discuss a protocol prior to it being performed, nor any stated goals for completing a paper review. Please add specific mechanisms for this process to the guidance.

In the same paragraph there is a requirement for a “...batch similar...” Similar needs to be defined within this context.

Please consider the following complete rewrite of the first two paragraphs in this section. It is simpler and clearer to refer to the required studies as the system exposure studies and leave the term PK out completely throughout this section except as noted. Much of the second paragraph is redundant and should be deleted.

“Plasma concentration-time studies should be used to evaluate systemic exposure for suspension drug products that produce sufficiently high drug concentration of the active ingredient and/or active moiety after nasal administration to obtain meaning AUC and Cmax data. The systemic exposure study may be one of the PK studies conducted to address clinical pharmacology and biopharmaceutics questions of regulatory interest. The systemic exposure study may be conducted in healthy subjects or SAR patients. The batch used for the systemic exposure study should be the one used in Section VI.C. If the batch is not one of the three batches used for the *in-vitro* BA studies (section V.A.1), *in-vitro* data should be provided for the PK batch using the same protocols as for the three batches.”

“For an NDA or an ANDA the systemic exposure study may be conducted with a replicate crossover or a nonreplicate crossover design. The study may be single or multiple doses. Several actuation’s from the drug product in each nostril...”

In the last sentence in this section we recommend that the wording be changed to give the sponsors the option of not conducting a pilot study as follows. “A pilot may be necessary to assess...”

Section VIII.A. It is stated that the "...sponsors should submit a protocol for a BE study with a pharmacodynamic or clinical endpoint..." As stated above, a mechanism needs to be created and described in the guidance for submitting protocols to OGD.

In the first sentence, the phrase "...for BA, or BE studies..." is unnecessary and should be deleted.

The phrases "...systemic BE..." and "...for a BE study. . ." should be replaced with the phrase "...systemic exposure study..."

The following change in wording is recommended to clarify that the requirement is for NDAs. "For an NDA, the study may be one..."

Section VIII.B. For clarity we recommend rewording the beginning of the first sentence in this section as follows. "If a blood level-time study is not performed then the recommended systemic absorption study design for..."

In the last sentence of this section, the text states that endpoints for placebo, test and reference treatments should be baseline-adjusted prior to statistical analysis. We suggest to use as a statistical approach an analysis of covariance (ANCOVA) on raw data with baseline used as a covariate. This approach has the advantage over baseline-adjustment analysis to adjust the data in a more general way.

Section VIII.C. For clarity and simplicity we recommend replacing this entire section with the following. "The batch requirements for this study are the same as those outlined above in Section VII."

IX.B.2. The proposed equivalence approach is population bioequivalence. However, many aspects are still unclear with this approach. The section on determination of the 95% confidence interval, for example, will need to be more detailed in the final guidance (ex. model needed to estimate the different variance terms and how to calculate the 95% CI).

For the *in-vitro* analyses, a comparison of the means using average bioequivalence and the limits of 90/111 might be sufficient. Our experience indicate that when the variances are not very high, which is the case for the *in-vitro* studies, average bioequivalence is a satisfactory approach and the variances are taking care off with the confidence intervals around the ratio of means.

IX. D. The statistical analysis proposed in the draft guidance for *in-vitro* BE data is quite unusual and complicated. Would a multivariate analysis with the profiles as the dependent vector and batch, canister and formulation as independent variables be of some interest? We would like to suggest this alternative because no matching triplets are required. The method proposed by the agency might induce some bias in the comparison and in the estimation of the upper bound.

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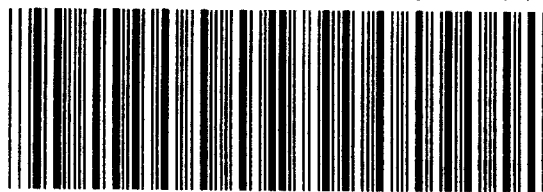
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